IRON/COPPER CO-CATALYZED C-C CROSS-COUPLING REACTION

A dissertation

Submitted in fulfillment

As a project work

For the Degree of

Master of Science in Chemistry

By

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Under the supervision of

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CONTENT

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All of yours sincerely,

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CERTIFICATE

This is to certify that the dissertation entitled, "**IRON/COPPER CO-CATALYZED C-C CROSS-COUPLING REACTION"** submitted by Swapna Sarita Mohapatra as a project work requirement for the award of Master of Science in Chemistry during the period of August2010- May2011 in the Department of Chemistry, National Institute of Technology, Rourkela is a record of authentic work carried out by her under my supervision and guidance.

To the best of my knowledge, the matter embodied in this project work has been submitted to National Institute of Technology, Rourkela for the award of Master of Science in Chemistry.

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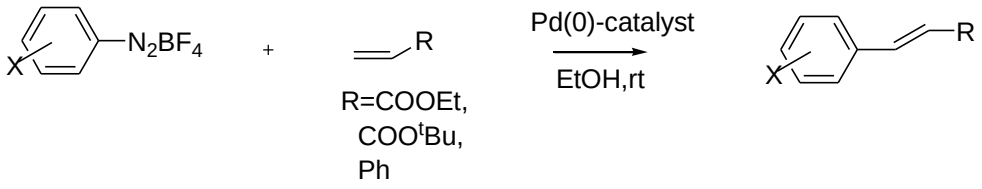
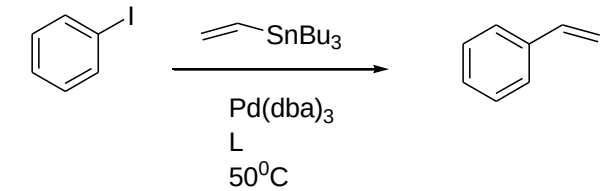
INTRODUCTION:

Development of carbon-carbon bond forming reactions forms the crux of modern synthetic organic chemistry. Of various methods developed for facilitating C-C bond formation, cross coupling reactions has been well explored. Initial attempt was made by using palladium catalyst for the C-C[1] cross coupling reactions. Among them some of the well known reactions are Heck reaction, Stille coupling, Miyaura-Suzuki coupling, Sonagashira coupling etc. The palladium(0)-catalyzed reaction of aryl and alkenyl halides with alkenes (the Heck reaction)[2-6] represents one of the most versatile tools in modern synthetic chemistry and has great potential for industrial applications. Here one of the recent application of the Heck reaction is the cross coupling reaction of aryl diazonium salt with activated alkenes in presence of Pd(0) catalyst.

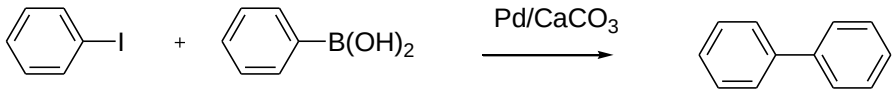


In the course of time the palladium-catalyzed coupling of organostannanes[7-11] with organic electrophiles, developed in recent years by Stille is rapidly becoming a very popular synthetic tool.

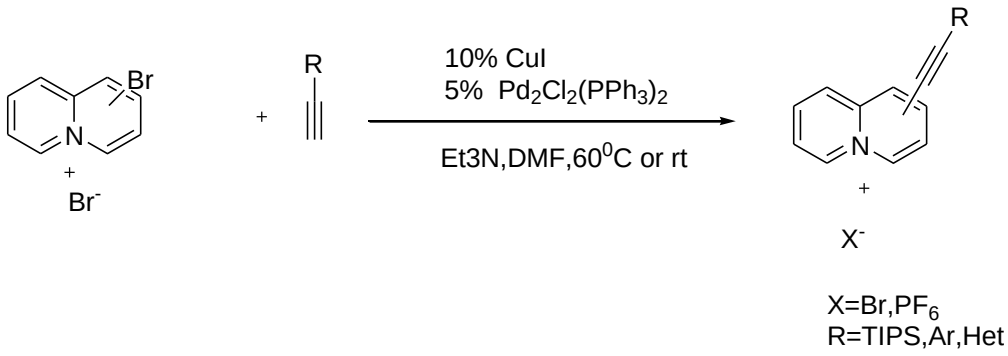


L=(p-MeO-$C_6H_5)_3P$

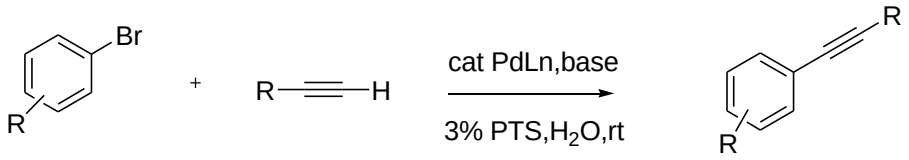
Miyaura-Suzuki[12-17] reactions, in particular, are very attractive due to the stability of the precursors, boronic acids, and facility of work up. The cross-coupling reactions occur between aryl halide and the organoboron compounds in presence of Pd (0) catalyst.



Aryl alkynes are important compounds for material sciences and medicinal chemistry[18]. These compounds are best obtained by the sonogashira-Hagihara[19-22] cross coupling reaction of terminal alkynes with aryl halides or triflates, originally using palladium catalysts together with phospine or diamine ligands.



Recently, an aryl bromide-terminal acetylene cross-coupling in water[23] at ambient temperatures is for the first time, allowed Sonogashira couplings to occur in the absence of both copper and organic solvents and at room temperature using commercially available reagents.



In some cases the Sonogashira reaction proceeds at ambient temperature (30 °C) in acetone or room-temperature ionic liquid, 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF4), as solvent under ultrasound irradiation to give enhanced reaction rates, excellent chemoselectivity, and high yields in the absence of a copper co-catalyst and a phosphate ligand.

In above case though Pd-based catalysts were frequently used, but these catalysts often treated as highly expensive and toxic in environmental point of view. Thus, replacement of Pd by less expensive and environmental friendly mental-catalyst is desired. Recently, copper-mediated coupling reactions have urged great attention in natural products and designed biomolecules synthesis. One of the reasons is the key discovery that copper based catalysts are less expensive and less toxic. Moreover, some organic derivatives can speed up the traditional copper-mediated coupling reaction and make these coupling reactions under mild conditions, which allow the copper-mediated coupling reaction to be used well in end game strategies on complex substrate.

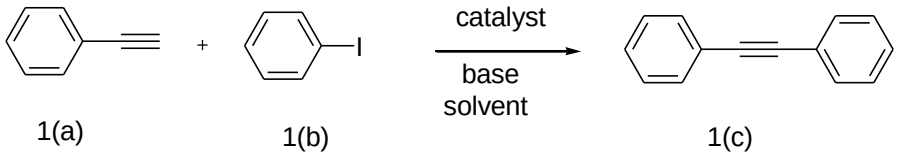
Meanwhile, ligand assisted[24-25]-copper-catalyzed C-C cross-coupling reactions with aryl halides have gained significant attention due to the low cost and relatively lower toxicity. Various ligands including diamines, amino acids, β-ketoesters, 1,10 phenanthroline derivatives, poly(ethylene glycol), ninhydin and other nitrogen- and/or oxygen-containing ligands, which chelates copper have been used for cross coupling reactions[26-33].

In order to replace ligands[34-35] and to use nontoxic catalysts in cross coupling reactions, lot of researches have been going on. With the tremendous effect heterogeneous catalyst came into existence for the C-C cross-coupling reactions. The discovery in 1954 by Kharash and Reinmuth[36], then in 1971 by Tamura and Kochi[37] that Grignard reagents and alkyl halides can be cross-coupled in the presence of iron catalysts has stimulated several studies toward the substitution of expensive and toxic transition metals and ligands by iron catalysts in C-C bond forming reactions. Highly dispersed Cu metal on alumina is a good catalyst for the cross-coupling of aryl iodides with phenylacetylene[38]. In the course of time it was found that aromatic iodides and terminal alkynes undergo C-C cross coupling reactions in the presence of iron salt and CuI as catalysts and relatively smooth conditions that do not

require the presence of expensive or toxic ligand. Recently, copper/Iron[39-45] co-catalytic systems were also successfully used for the cross-coupling reactions under homogeneous conditions considering the cheap and environment friendly behavior of iron[46]. Hence we envisaged to utilize, Cu/Fe co-catalytic system in a more-wider way to synthesize the cross-coupling reactions of aryl halides and phenyl acetylene.

The main objective of our present study is to develop a suitable catalytic system for the cross-coupling reactions using non-expensive and nontoxic catalysts which will also not require the presence of toxic ligands. (Scheme-1).

Scheme 1:

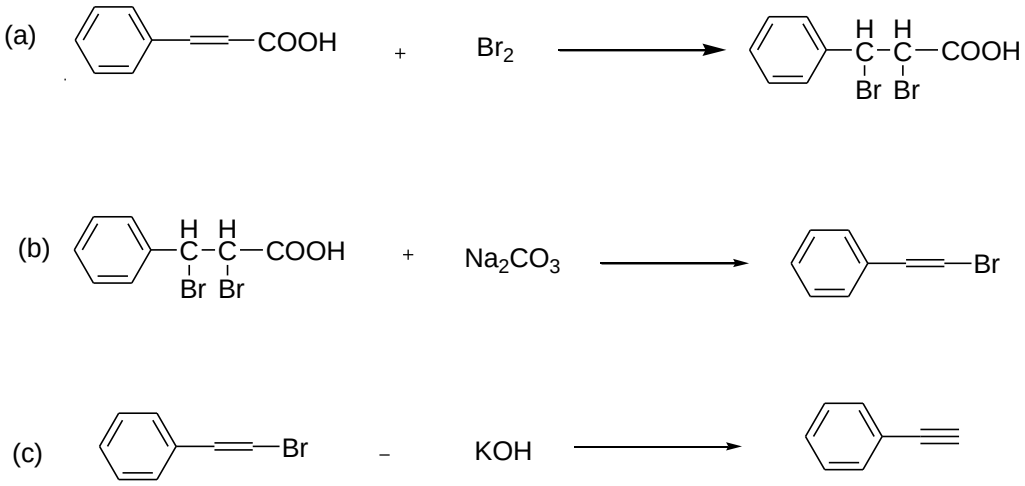


1(a) 1(b) 1(c)

RESULTs and Discussions:

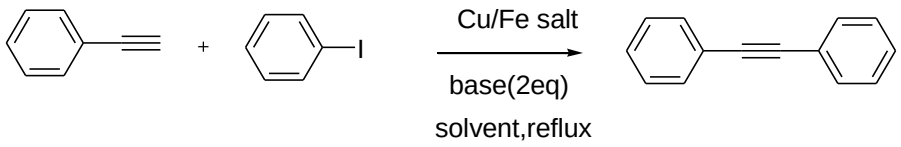
Initially, we prepared the phenyl acetylene by following the standard procedure reported elsewhere (Scheme 2). Cinnamic acid on treatment with bromine gave 2, 3-dibromo-3-phenylpropanoic acid which on heating with aqueous sodium carbonate solution gave β-bromostyrene. β-bromostyrene on heating with potassium hydroxide lead to phenylacetylene in good yield.

Scheme 2:



Then we used phenylacetylene and iodobenzene as coupling partners in the presence catalyst. We took different combination of copper and iron sources as catalyst for cross-coupling reactions in presence of different bases. The reactions were carried out in dry DMF at its boiling temperature (151 °C). Our results are summarized in table 1. We observed that the combination of CuI and $Fe(NO_3)_3$ served as a better catalytic system for the cross-coupling of phenylacetylene with iodobenzene to give diphenylacetylene.

TABLE-1:



Entry	Reagent Used	Catalyst	Co-Catalyst	Solvent	Base	Time Taken	Yield
1	Phenyl-acetylene	CuI (10%mol)	$FeCl_3$	DMF	K_2CO_3	21h	10%
2	Phenyl-acetylene	CuO (10%mol)	$FeCl_3$	DMF	t-BuOK	21h	40%
3	Phenyl-acetylene	CuCl (10%mol)	$FeCl_3$	DMF	t-BuOK	21h	13.3%
4	Phenyl-acetylene	CuI (10%mol)	$Fe(NO_3)_3$	DMF	t-BuOK	21h	56.9%

CONCLUSION:

In conclusion, we have demonstrated a ligand-free catalytic system for the C-C cross-coupling of phenyl acetylene with aryl halides. The synergistic effects of iron and copper for the alkynylation were exploited. This catalytic process is simple, and environmentally safe. Further investigation on the development of more suitable catalytic system for C-C cross-coupling that is in progress.

EXPERIMENTAL SECTION:

Preparation of diphenylacetylene:

Phenyl acetylene (1eq, 1.47mmol), t-BuOK(2eq, 2.94mmol) in dry DMF were refluxed for 21hrs under argon atmosphere. Catalyst and co-catalyst were added as per (table1, entry1-8).Then aryl iodide(1eq, 1.47mmol) was added to the reaction . After 21hrs, the reaction mixture was worked-up with ethyl acetate and washed with brine solution. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, 100 g, PET(100% by V)) to give Diphenyl acetylene.oct-2-yn-1-one. For yield and time of completion refer (table1, entry1-8).

Preparation of Phenyl Acetylene:

(74gm, 0.5mol) of cinnamic acid in 300ml of hot DCM in a 500ml flask was dissolved and the solution was cooled in ice-water with shaking. As soon as the solid began to crystallize out,a solution of (80gm,26ml,0.5mol) of bromine in 50ml of DCM was added rapidly in three portions with vigorous shaking and cooling.The flask and the contents was allowed to stand in an ice- bath for 30 mins to allow complete crystallization of the product. The latter was collected by filtration.

A pure specimen of 2, 3-dibromo-3-phenylpropanoic acid (m.p204°C).The bulk of the crude bromoacid under reflux with 750ml of 10% aqueous sodium carbonate solution was boiled, cooled and the layer of crude β-bromostyrene. The aqueous phase was extracted with two 75ml portions of ether, the extract was combined with the organic phase, dried over anhydrous calcium chloride and the ether was removed on a rotary evaporator. About 65-70gm of crude β-bromostyrene was obtained.

100gm of potassium hydroxide pellets in a 500ml flask was placed, the pellets were moistened with about 2ml of water and the flask was fitted with a still-head carrying a dropping funnel and a condenser was set for downward distillation. The flask was heated in a oil bath maintained at 200° C and the crude β-bromostyrene was added dropwise onto the molten alkali at a rate of about 1drop per sec .Phenyl acetylene began to distil over,slowly the

bath temperature was raised to about 220°C and it was kept at this point until the addition was complete. Then it was continued to heat at about 230°C until no more product distilled over. The upper layer of the distillate was separated, dried over potassium hydroxide pellets and redistilled. The phenyl acetylene was collected at 142-144°C; yield is 25gm (49%).

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